# Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Protocol

## 1. Title of project

SonoVue® (sulphur hexafluoride microbubbles) – contrast agent for contrast enhanced ultrasound in liver imaging.

## 2. Name of External Assessment Group (EAG) and project lead

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**Plain English Summary**

Medical imaging, including ultrasound scanning, is important in diagnosing and planning treatment for a wide range of conditions including liver disease. Liver imaging will sometimes identify focal abnormalities in the liver which cannot be characterised initially and may need another test to fully explain the abnormality. The main aim of this subsequent liver imaging is to distinguish between liver cancers and benign abnormalities, which is not likely to require further treatment. Cancer in the liver is relatively rare and expert opinion suggests that 70 to 75% of liver abnormalities investigated in the NHS are found to be benign. One important factor in selecting an imaging test is ability to provide a rapid diagnosis, both to facilitate prompt treatment in patients who do have cancer and to minimise anxiety in the majority who do not. Most liver lesions are found at an initial ultrasound scan. If the liver abnormality is not characterised by this test, the patient is usually referred for additional imaging using magnetic resonance imaging (MRI) and/or computed tomography (CT). This can lead to waits of several months with consequent distress to patients and families. In addition, there are potential drawbacks in using these other imaging techniques. CT uses ionising radiation and the intravenous contrast agent can, on rare occasions, cause kidney damage. Some patients cannot have an MRI scan due to pacemakers and others find the examination causes claustrophobia.

Imaging technology has developed very rapidly in recent years and contrast agents have been developed for use with ultrasound scanning. These contrast agents are injected, but remain in the patient's blood and are broken down by the body after a few minutes and breathed out as a gas. The use of contrast agents may improve the ability of ultrasound to distinguish between cancer in the liver and benign liver abnormalities and, because contrast enhanced ultrasound can be performed at the same appointment as conventional ultrasound, more rapid diagnoses may be possible and some CT and MRI examinations may be avoided.

The purpose of this project is to assess the benefits, risks and cost-effectiveness of contrast enhanced ultrasound using SonoVue® (Bracco UK Ltd) for the assessment of liver damage in adult patients.

## 3. Decision problem

### 3.1. Objectives

To evaluate the clinical and cost effectiveness of contrast enhanced ultrasound (CEUS) using the contrast agent SonoVue® for the assessment of adults with focal liver lesions (FLL), in whom un-enhanced ultrasound or other liver imaging is inconclusive.

### 4.2. Intervention technologies

SonoVue® (Bracco UK Ltd) is a contrast agent involving sulphur hexafluoride microbubbles for contrast enhanced ultrasound (CEUS) imaging in adults. It is used to enhance the echogenicity of the blood and can thus improve the signal to noise ratio in ultrasound. SonoVue® should only be used in patients where un-enhanced ultrasound is inconclusive.

SonoVue® product information lists its applications as:

- Echocardiography – provision of opacification of cardiac chambers and enhancement left ventricular echocardial border delineation in patients with suspected or known cardiovascular disease.

- Doppler ultrasound of the macrovasculature – detection or exclusion of abnormalities in the cerebral arteries, extra-cranial carotid arteries, or peripheral arteries.

- Doppler ultrasound of the microvasculature – visualising the vascularity of liver and breast lesions for lesion characterisation.

The focus of this assessment is CEUS of the liver.

SonoVue® consists of a kit containing a vial of sulphur hexafluoride gas and phospholipid powder, a pre-filled syringe of solvent (sodium chloride solution) and a transfer and ventilation system (mini spike). The saline is introduced into the vial by the mini spike delivery system and once reconstituted, microbubbles are formed. These microbubbles are the contrast agent which is injected into a peripheral vein at the ante cubital fossa. When the ultrasound probe is placed on the abdomen, ultrasound waves cause the microbubbles to resonate so that a signal is picked up by a transducer and an image is formed on a screen.

As this contrast agent is a pure blood pool agent it remains within the patient's blood vessels and, depending on the type of lesion, it shows a pattern of uptake similar to that of CT or MRI contrast agents. Generally for benign lesions the lesion will remain bright or isoechoic with the rest of the liver. For malignant lesions the area will wash out and leave a black hole.

The contrast agent is broken down by the body after a few minutes and the sulphur hexafluoride gas is exhaled through the lungs and the phospholipid component of the microbubble shell is metabolised (re-entering the endogenous phospholipid metabolic pathway). The adverse event rate associated with the use of SonoVue® for liver imaging is

likely to be similar to or lower than that associated with other imaging modalities (CECT or CEMRI); a post-marketing study, published in 2006, included 23,188 abdominal investigations and reported adverse events in 29 cases, of which only two were graded as serious.[1]

SonoVue® is a second generation contrast agent. These agents have a flexible shell which allows continuous imaging (at a low mechanical index) without early destruction of the microbubble. First generation agents have now been superseded by second generation agents and are no longer available in Europe.

Other similar ultrasound contrast agents (e.g. Luminity®, Lantheus Medical Imaging and Optison®, GE Healthcare) are indicated for use in echocardiography only. Therefore, no equivalent alternative technologies will be considered in this assessment.

### 4.3. Population

The indication for this assessment is the detection and characterisation of FLLs in adults and the target condition is malignancies of the liver.

In this context, the term focal lesion in the liver refers to any focal area of perceived difference seen on an imaging study occurring in one specific area of the liver. FLLs can be broadly as benign (haemangioma, focal nodular hyperplasia, focal fatty infiltration or sparing and adenoma) or malignant (primary hepatocellular carcinoma, cholangiocarcinoma or liver metastases), with the detection or exclusion of malignancy being the primary aim of diagnostic imaging. The distinction between benign and malignant determines the individual's prognosis and the subsequent treatment strategy. Benign, asymptomatic liver lesions usually do not require any treatment. Depending on the specific type of lesion, the individual may be monitored and the lesion rescanned in 6 to 12 months. Once a malignant lesion is identified it is important to distinguish between primary and secondary cancers as this is likely to impact how the individual is managed. Malignant lesions may be treated by a range of interventions including chemotherapy, liver resection (surgery), and local ablative therapy. The treatment of primary hepatocellular carcinoma has been addressed in published guidelines,[2, 3] and NICE has issued guidance on a number of individual interventions for primary hepatocellular carcinoma and liver metastases (see Appendix 1). However, expert opinion suggests that practice within the NHS may vary significantly across regions based on clinician preference.

Although liver cancer is rare in the UK, (age-standardised rates are 4.7 per 100,000 males and 2.9 per 100,000 females)[4] it is the second fastest increasing cancer in males and the third fastest in females, (increases of 38% and 28%, respectively, in the last decade).[5] In addition, expert opinion suggests that as many as 70 to 75% of FLLs assessed in the NHS may be benign. One possible benefit of CEUS may therefore be rapid rule-out of malignancy, with associated reduction in anxiety for patients and families; current practice of referring patients with inconclusive un-enhanced ultrasound for contrast enhanced magnetic resonance imaging (CEMRI) and/or contrast enhanced computed tomography (CECT), may result in a wait of several months.

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) produced guidelines and good clinical practice recommendations for CEUS in 2004. The latest version of the guidelines was published in 2008.[6] The 2008 version of the EFSUMB guidelines are currently being updated. The 2008 EFSUMB guidelines recommend the use of CEUS for the characterisation of FLL in the following indications:

- patients with incidental findings on routine ultrasound
- investigation of lesions or suspected lesions in chronic hepatitis or liver cirrhosis
- investigation of lesions or suspected lesions in patients with a history of malignancy
- patients with inconclusive MRI/CT or cytology/histology results
- characterisation of portal vein thrombosis

and for the detection of FLL in the following indications:

- to rule-out liver metastases
- in selected cases, when clinically relevant for treatment planning and as a complement to CECT and/or CEMRI, to assess the number and location of liver metastases
- surveillance of patients with known malignancy
- suspected cholangiocarcinoma, where other imaging is inconclusive
- suspected liver trauma (in some situations)

Because SonoVue® should be used only where un-enhanced ultrasound is inconclusive, we consider its primary application to be for the characterisation of lesions (benign or malignant) in patients with known FLLs; most patients who have already undergone un-enhanced ultrasound and who have proceeded to CEUS are likely to have FLLs (seen at un-enhanced ultrasound), the nature of which remains uncertain. Other, relevant applications include the detection of specific types of malignant FLL (e.g. liver metastases, recurrent or residual disease following treatment of a known malignancy). CEUS may also identify addition FLLs over and above those detected on un-enhanced ultrasound. A recent systematic review reported ranges for the sensitivity and specificity of SonoVue® CEUS for the detection of liver metastases as 79% to 100% and 95% to 100% respectively,[7] and initial scoping searches have identified studies assessing the accuracy of SonoVue® CEUS for the detection of residual disease post-treatment.[8, 9]

### 4.4. Relevant comparators

Patients with inconclusive un-enhanced ultrasound are currently referred for CECT and/or CEMRI. The comparators for this assessment are therefore CECT and CEMRI. A recent

systematic review compared the accuracy of SonoVue® CEUS, CECT and CEMRI for the differentiation of malignant and benign liver lesions. The reported sensitivities were 88% (95% CI 79% to 84%), 90% (95% CI 88% to 92%) and 86% (95% CI 83% to 88%), respectively, and the corresponding specificities were 81% (95% CI 79% to 84%), 77% (95% CI 71% to 82%) and 81% (95% CI 76% t 85%).[10] However, these data were based on indirect comparisons. CEUS could be included in the diagnostic pathway as a replacement for CECT/CEMRI (Figure 1), or as a triage step to reduce the use of CECT/CEMRI (Figure 2).

**Figure 1: Diagnostic algorithm for liver imaging - CEUS as a replacement test for CECT/CEMRI**

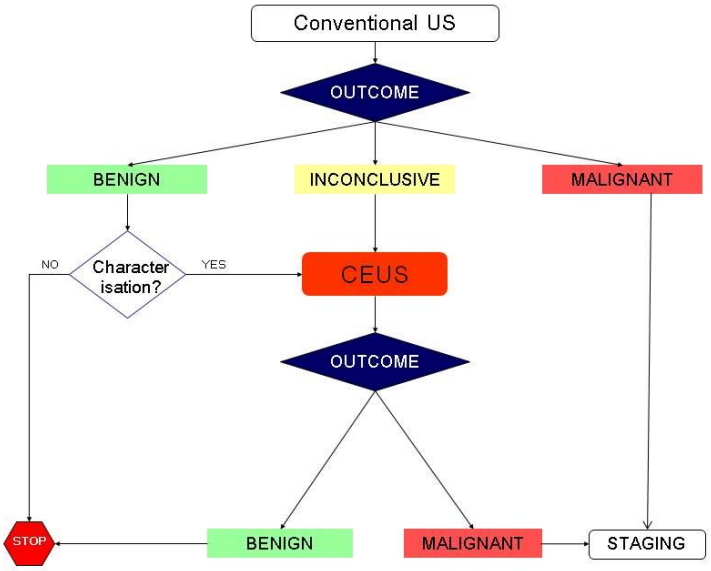
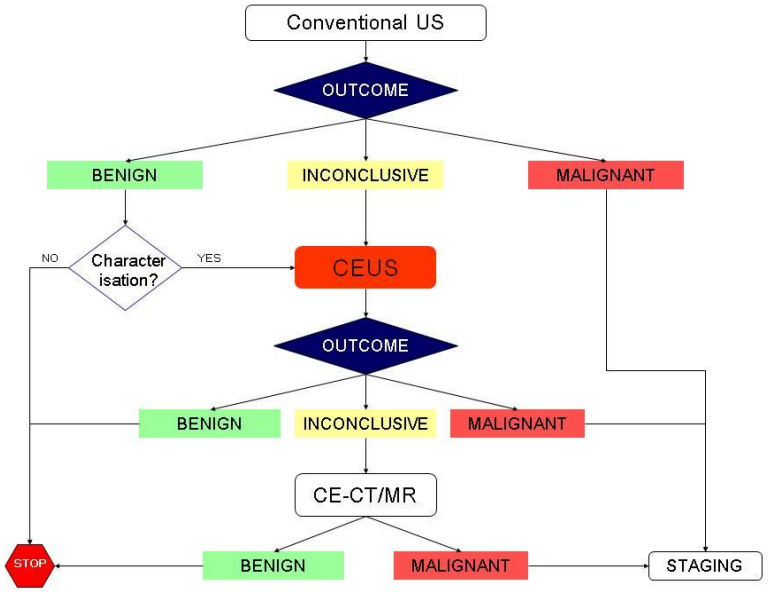



**Figure 2: Diagnostic algorithm for liver imaging - CEUS as a triage test to reduce the use of CECT/CEMRI**



Expert opinion has indicated that biopsy would not be performed on the basis of un-enhanced ultrasound examination alone, therefore, biopsy alone is not a relevant comparator for CEUS.

## 5. Report methods for assessing clinical effectiveness

A systematic review will be conducted to summarise the evidence on the clinical effectiveness of SonoVue® CEUS for the assessment of focal liver lesions in adults in whom liver imaging with un-enhanced ultrasound has been inconclusive. Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[11] and NICE Diagnostic Assessment Programme interim methods statement. [12]

### 5.1. Inclusion and exclusion criteria

*Participants*

Study populations eligible for inclusion will be:

Adults (≥18 years) in whom liver imaging with un-enhanced ultrasound or other liver imaging has been inconclusive, including patients being assessed for:

- Suspected primary hepatocellular carcinoma
- Suspected secondary malignancy (liver metastases)
- Response to treatment/recurrence of known liver malignancy

*Setting*

Relevant settings are secondary or tertiary care.

*Interventions (index test(s))*

SonoVue® CEUS

*Comparators*

Comparators eligible for inclusion will be:

- Contrast enhanced computed tomography (CECT)
- Contrast enhanced magnetic resonance imaging (CEMRI)

*Reference standard*

The reference standard for a positive diagnosis will be histology following biopsy or surgical excision. Patients who test negative on the index test will generally not undergo biopsy or surgical treatment; clinical/radiological follow-up for a minimum of six months will therefore be considered an acceptable reference standard in these patients.

*Outcomes*

The following outcomes will be considered:

- Effect of testing on treatment plan (e.g. surgical or medical management, or palliative care), where information on the appropriateness of the final treatment plan is also reported
- Effect of testing on clinical outcome, (e.g. overall survival, progression free survival)
- Prognosis- the ability of test result to predict clinical outcome (e.g. overall survival, progression free survival, response to treatment)
- Test accuracy and number of patients/lesions classified as non-diagnostic by SonoVue® CEUS.

For included studies reporting any of the above outcome measures, the following outcomes will also be considered if reported:

- Acceptability of tests to patients or surrogate measures of acceptability (e.g. waiting time and associated anxiety).
- Adverse events associated with testing (e.g. claustrophobia, reaction to contrast media).
- Additional FLLs detected by CEUS, over and above those seen on un-enhanced ultrasound.

Radiation exposure is not considered a relevant outcome, as the population is mostly older adults in whom additional incident cancers due to imaging-related radiation are likely to be minimal. In addition a previous technology assessment (new generation CT for cardiac imaging) showed that including radiation exposure in modelling did not influence the results of cost-effectiveness analyses. [13]

*Study design*

The following types of studies will be included:

- Randomised or non-randomised controlled trials, where participants are assigned to the intervention or comparator tests, for treatment planning, and outcomes are compared at follow-up.
- Observational studies which report the results of multi-variable regression modelling with clinical outcome (e.g. survival, response to treatment) as the dependent variable and index test and comparator test results as independent variables. Included studies should control adequately for potential confounders (e.g. age, tumour stage, previous treatment, results of other imaging).
- Test accuracy studies, where the index test is compared with one or more of the comparators and the reference standard. Test accuracy studies of the index test alone will be included if they are conducted in patients who have previously undergone one or more of the comparator tests (e.g. a study of the accuracy of Sonovue for the diagnosis of HCC in patients with inconclusive findings on CECT), as these studies may inform cost-effectiveness modelling.

Test accuracy studies, will be required to report the absolute numbers of true positive, false negative, false positive, and true negative index test results, or sufficient information to allow their calculation. If data are incomplete, study authors will be contacted to seek clarification, where practical.

The following study/publication types will be excluded:

- Pre-clinical and animal
- Reviews, editorials, and opinion pieces
- Case reports
- Studies reporting only technical aspects of the test, or image quality
- Studies with <10 participants

### 5.2. Search strategy

Search strategies will be based on target condition and intervention, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[11, 14, 15] Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life will also be included, see Section 6 for further detail.

The following databases will be searched for relevant studies from 2000 to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR ) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (Internet)
- Health Technology Assessment Database (HTA) (Internet)
- Science Citation Index (SCI) (Web of Science)
- NIHR Health Technology Assessment Programme (Internet)

Completed and ongoing trials will be identified by searches of the following resources (2000-2011):

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- Current Controlled Trials (http://www.controlled-trials.com/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/)

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. These may include British Medical Ultrasound Society, European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) EUROSON congress.
Identified references will be downloaded in Endnote X4 software for further assessment and handling.

References in retrieved articles and relevant systematic reviews will be checked.
Search strategies will be developed specifically for each database and the keywords associated with liver malignancies shall be adapted according to the configuration of each database.

No restrictions on language or publication status will be applied. Limits will be applied to remove animal and phantom studies. Searches will take into account generic and other product names for the intervention. Examples of the search strategies to be used are presented in Appendix 1; these will be adapted as necessary following consultation with clinical experts.

### 5.3. Data extraction strategy

Two reviewers will independently screen titles and abstracts of all reports identified by searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Data relating to study details, participants, intervention and comparator tests, reference standard, and outcome measures will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

### 5.4. Quality assessment strategy

The methodological quality of included studies will be assessed using standard tools. [11]The QUADAS tool,[16, 17] has been recommended for assessing the methodological quality of test accuracy studies.[11, 14] A revised version of QUADAS (QUADAS-2) has recently been released www.QUADAS.org. [18] QUADAS-2 more closely resembles the approach and structure of the Cochrane risk of bias tool. The QUADAS-2 tool will be used in this assessment.

The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. In addition, if enough data are available from the included studies, quality components will be included as covariates in

SROC models, to investigate their possible association with test performance. Based on the findings of the quality assessment, recommendations will be made for the conduct of future studies.

### 5.5. Methods of analysis/synthesis

The results of initial scoping searches suggest that trial data and prognostic data are likely to be sparse or non-existent. This section therefore focuses on the synthesis of data from test accuracy studies. If other studies are identified, we anticipate that these will be summarised in a narrative synthesis.

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by clinical application (diagnosis of primary hepatocellular carcinoma, diagnosis of liver metastases, assessment of treatment response/recurrence).

Any data included on the following outcome measures: effects of testing on treatment planning and/or clinical outcome; adverse events associated with testing; acceptability to patients will be summarized according to the size and range of the outcomes reported. For test accuracy data, absolute numbers of true positive, false negative, false positive and true negative test results, as well as sensitivity and specificity values, with 95% confidence intervals will be presented for each study and patient group reported.

Where appropriate, and where sufficient accuracy data are available, summary receiver operating characteristic (SROC) curves will be calculated to summarise test accuracy data. SROC modelling will use the bivariate approach.[19-21] Potential sources of heterogeneity will be investigated by extending SROC models to include study level covariates, (e.g. participant age, tumour stage, hepatitis status, cirrhosis status); the bivariate approach to modelling allows investigation of the effects of covariates on sensitivity and specificity separately. Where data are insufficient to support meta-analyses, the following graphical representations will be presented: plots in ROC space (without summary curves) for test accuracy data; forest plots for any trial data.

A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

## 6. Report methods for synthesising evidence of cost-effectiveness

## 6.1 Identifying and reviewing published cost-effectiveness studies

Exploration of the literature regarding published economic evaluations, utility studies and cost studies will be performed in the literature databases listed above. In addition, specific health economic databases will be searched (e.g. NHSEED (NHS Economic Evaluation Database), and HEED (Health Economic Evaluation Database); an example search strategy is included in Appendix 1. Searches will focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses, either studying the diagnostic phase (patients with FLLs and inconclusive un-enhanced ultrasound), therapeutic phase (patients with liver malignancy), or a combination. For our assessment cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model and estimation of model input parameters that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.[12] Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

## 6.2 Evaluation of costs, quality of life and cost-effectiveness

Decision analytic modelling will be undertaken to determine the cost-effectiveness of SonoVue® CEUS for the assessment of focal liver lesions in adults in whom liver imaging with un-enhanced ultrasound has been inconclusive. The analysis will consider the consequences of diagnostic accuracy, treatment planning, and QALYs.

*Potential diagnostic strategies*

Depending on the nature of the FLL and local practice within the NHS a range of typical diagnostic strategies may emerge as current practice, which may include CECT and/or CEMRI.

The following possible diagnostic strategies arise when assessing the role of CEUS for the assessment of focal liver lesions in adults in whom liver imaging with un-enhanced ultrasound has been inconclusive:

- CEUS
- CEUS* → CECT

- CEUS* → CEMRI

* Additional examination, to be conducted if previous one was not conclusive.

Comparators to be included in the model may depend on the availability of data.

*Model structure*
Published studies that measure the clinical utility of SonoVue® CEUS from initial diagnosis through to final health outcomes have not been identified during the scoping phase. Consequently, it is likely that a linked evidence approach will need to be used in the modelling. That is, outcomes of the diagnostic tests to be assessed will need to be related to changes in treatment decisions, any delays in diagnosis and final heath outcomes. Necessary choices and definitions regarding the structure of the model will depend on the findings from the literature review and consultation with clinical experts. In addition, the existence/availability of any other electronic models that reflect the cost-effectiveness of treatment pathways for these patients, and are representative of current care within the NHS, will be determined.
Issues relevant to analyses:

- Longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the models which are based on expert opinion.
- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

A simple draft model structure is presented ( Appendix 3); this may be developed/expanded as indicated (Appendix 3) and as available data allow.

*Health outcomes*
Utility values, based on literature or other sources, will be incorporated in the economic model. QALYs will be calculated from the economic modelling.

*Costs*
Resource utilisation will be estimated for the diagnostic tests and treatments. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the comparators.

## 7. Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 05/12/2011. Data arriving after this date will not be considered. If the data

meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.
Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

**8. Competing interests of authors**

None

**9. Timetable/milestones**

| **Milestones** | **Completion data** |
|---|---|
| Draft protocol | 16/09/2011 |
| Final protocol | 14/10/2011 |
| Progress report | w/c 05/12/2011 |
| Draft assessment report | 27/01/2012 |
| Final assessment report | 27/02/2012 |

## 10. References

[1] Piscaglia F, Bolondi L. The safety of Sonovue in abdominal applications: Retrospective analysis of 23188 investigations. *Ultrasound Med Biol* 2006;32(9):1369-1375.

[2] Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42(5):1208-36.

[3] Ryder S, Hepatocellular UK Group. *UK Guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults (revised edition)*. Nottingham: Nottingham University Hospitals NHS Trust, 2009. 57p.

[4] Office for National Statistics. *Cancer statistics registrations: registrations of cancer diagnosed in 1999, England (Series MB1 no. 30)*. London: ONS, 2002.

[5] Cancer Research UK. Cancer incidence for common cancers - UK statistics [Internet]. London: Cancer Research UK, 2011 [cited 14.9.11]. Available from: http://info.cancerresearchuk.org/cancerstats/incidence/commoncancers/

[6] Claudon M, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) - update 2008. *Ultraschall Med* 2008;29(1):28-44.

[7] Cabassa P, Bipat S, Longaretti L, Morone M, Maroldi R. Liver metastases: Sulphur hexafluoride-enhanced ultrasonography for lesion detection: a systematic review. *Ultrasound Med Biol* 2010;36(10):1561-7.

[8] Vilana R, Bianchi L, Varela M, Nicolau C, Sanchez M, Ayuso C, et al. Is microbubble-enhanced ultrasonography sufficient for assessment of response to percutaneous treatment in patients with early hepatocellular carcinoma? *Eur Radiol* 2006;16(11):2454-62.

[9] Wang J-H, Lu S-N, Tung H-D, Changchien C-S, Hung C-H, Chen C-H, et al. Flash-echo contrast sonography in the evaluation of response of small hepatocellular carcinoma to percutaneous ablation. *J Clin Ultrasound* 2006;34(4):161-8.

[10] Guang Y, Xie L, Ding H, Cai A, Huang Y. Diagnosis value of focal liver lesions with SonoVue-enhanced ultrasound compared with contrast-enhanced computed tomography and contrast-enhanced MRI: a meta-analysis. *J Cancer Res Clin Oncol* 2011.

[11] Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [cited 7.6.11] Available from: http://www.york.ac.uk/inst/crd/systematic_reviews_book.htm

[12] National Institute for Health and Clinical Excellence. *Diagnostics Assessment Programme: interim methods statement (version 2) [Internet]*. London: NICE, 2010 [cited 12.1.11]. 46p. Available from: http://www.nice.org.uk/media/164/3C/DAPInterimMethodsStatementProgramme.pdf

[13] Westwood M, Al M, Burgers L, Redekop W, Lhachimi S, Armstrong N, et al. *Computed tomography (CT) scanners for cardiac imaging – Somatom Definition Flash, Aquilion One, Brilliance iCT and Discovery CT750 HD: a Diagnostic Assessment Report [Internet]*. York: Kleijnen Systematic Reviews Ltd., 2011 [cited 14.9.11]. 336p. Available from: http://guidance.nice.org.uk/nicemedia/live/13243/56230/56230.pdf

[14] Cochrane Diagnostic Test Accuracy Working Group. *Handbook for DTA Reviews [internet]*: Cochrane Collaboration, 2011 [cited 12.1.11] Available from: http://srdta.cochrane.org/handbook-dta-reviews

[15] Whiting P, Westwood M, Beynon R, Burke M, Sterne JA, Glanville J. Inclusion of methodological filters in searches for diagnostic test accuracy studies misses relevant studies. *J Clin Epidemiol* 2011;64(6):602-7.

[16] Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;3:25.

[17] Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. A systematic review of sources of variation and bias in studies of diagnostic accuracy. *Ann Intern Med* 2004;140:189-202.

[18] Whiting P, Rutjes AW, westwood M, Mallet S, Deeks JJ, Reitsma JB, et al. The development of QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011:In press.

[19] Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PMM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;58:982-90.

[20] Harbord RM, Deek JJ, Egger M, Whiting P, Sterne JA. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2007;8(2):239-51.

[21] Harbord RM, Whiting P, Sterne JA, Egger M, Deeks JJ, Shang A, et al. An empirical comparison of methods for meta-analysis of diagnostic accuracy showed hierarchical models are necessary. *J Clin Epidemiol* 2008;61(11):1095-103.

## Appendix 1

## Clinical effectiveness search

### Medline (OvidSP): 2000-2011/09/wk 1
### Searched 15.9.11

1 neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (78927)
2 (Metasta$ or meta-sta$).ti,ab,ot,hw. (309063)
3 or/1-2 (311269)
4 (liver or hepato$ or hepatic$).ti,ab,ot,hw. (864813)
5 3 and 4 (45882)
6 exp Liver Neoplasms/ (112164)
7 exp Bile Duct Neoplasms/ (11889)
8 Carcinoma, Hepatocellular/ (50647)
9 (FLL or FLLs).ti,ab,ot. (95)
10 Cholangiocarcinoma/ (4109)
11 ((liver$ or hepat$) adj3 (cancer$ or met$ or malignan$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$ or angiosarcoma$)).ti,ab,ot,hw. (168313)
12 (hepatoma$ or h?emangiosarcoma$ or h?emangio-sarcoma$).ti,ab,ot,hw. (27634)
13 (Focal liver lesion$ and (cancer$ or met or mets or metasta$ or malignan$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$ or angiosarcoma$)).ti,ab,ot,hw. (711)
14 (BFLL or BFLLS).ti,ab,ot. (3)
15 (HCC or HCCs).ti,ab,ot. (18590)
16 (Cholangiocarcinoma$ or Cholangio-carcinoma$).ti,ab,ot,hw. (6158)
17 (Bile duct$ adj3 (cancer$ or met$ or malignan$ or lesion$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$)).ti,ab,ot,hw. (14419)
18 or/5-17 (198600)
19 ultrasonography/ or ultrasonography, doppler/ or exp ultrasonography, doppler, duplex/ or exp ultrasonography, doppler, pulsed/ (89506)
20 ((ultrasonic$ or ultra-sonic$) adj4 (scan or imag$ or echogram$ or sonogra$ or detect$ or diagnos$ or exam$)).ti,ot,ab,hw. (6793)
21 (ultraso$ or ultra-so$ or sonogra$ or Echotomogra$ or Echo-tomogra$ or echoscope$ or echosound$ or Echogra$ or tomoechogra$ or tomo-echogra$).ti,ot,ab,hw. (274775)
22 or/19-21 (279114)
23 Sulfur Hexafluoride/ (1474)
24 (hexafluoruro-sulfurico or SF6 or SF-6 or sulphur hexafluoride$ or sulphur hexafluoride$ or sulfur hexafluoride$ or sulfur hexafluoride$).af. (2133)
25 or/23-24 (2133)
26 22 and 25 (658)
27 (Sonovue or sono-vue or Sonavoid or Sonogen or sonagen or Sonavist).af. (499)
28 (CE-US or CEUS).ti,ab,ot. (516)
29 ((hexafluoruro-sulfurico or SF6 or SF-6) adj4 (US or ultraso$ or ultra-so$ or sonogra$ or Echotomogra$ or Echo-tomogra$ or echoscop$ or echosound$ or Echogra$ or tomoechogra$ or tomo-echogra$ or imag$)).af. (7)
30 ((Sulfur or Sulphur) adj2 (hexafluoride$ or hexa-fluoride$) adj4 (US or ultraso$ or ultra-so$ or sonogra$ or Echotomogra$ or Echo-tomogra$ or echoscop$ or echosound$ or Echogra$ or tomoechogra$ or tomo-echogra$ or imag$)).af. (28)
31 (SF6US or SF6-US or SF-6US or SF-6-US).af. (0)

32 ((SF6 or SF6 or sulphur hexafluoride$ or sulphur hexafluoride$ or sulfur hexafluoride$ or sulfur hexafluoride$) adj4 (bubbl$ or microbubbl$ or micro-bubbl$ or micropartic$ or micro-partic$)).af. (213)
33 or/27-32 (991)
34 26 or 33 (1183)
35 18 and 34 (365)
36 exp Liver Neoplasms/us (2702)
37 Carcinoma, Hepatocellular/us (1258)
38 exp Bile Duct Neoplasms/us (375)
39 Cholangiocarcinoma/us (137)
40 Neoplasm Metastasis/us (51)
41 Neoplasm Seeding/ra (1)
42 Neoplasms, Unknown Primary/us (21)
43 or/36-42 (3089)
44 25 and 43 (162)
45 35 or 44 (366)
46 limit 45 to yr="2000 -Current" (361)
47 animals/ not (animals/ and humans/) (3586762)
**48 46 not 47 (340)**

**Economic evaluations search**

**Medline (OvidSP): 2000-2011/09/wk 1**
**Searched 15.9.11**

1 economics/ (26160)
2 exp "costs and cost analysis"/ (159824)
3 economics, dental/ (1851)
4 exp "economics, hospital"/ (17418)
5 economics, medical/ (8505)
6 economics, nursing/ (3853)
7 economics, pharmaceutical/ (2276)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (345758)
9 (expenditure$ not energy).ti,ab. (14613)
10 (value adj1 money).ti,ab. (20)
11 budget$.ti,ab. (14766)
12 or/1-11 (459756)
13 ((energy or oxygen) adj cost).ti,ab. (2351)
14 (metabolic adj cost).ti,ab. (614)
15 ((energy or oxygen) adj expenditure).ti,ab. (13513)
16 or/13-15 (15852)
17 12 not 16 (456159)
18 letter.pt. (726087)
19 editorial.pt. (283742)
20 historical article.pt. (279927)
21 or/18-20 (1276679)
22 17 not 21 (431461)
23 neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (78927)
24 (Metasta$ or meta-sta$).ti,ab,ot,hw. (309063)
25 or/23-24 (311269)
26 (liver or hepato$ or hepatic$).ti,ab,ot,hw. (864813)
27 25 and 26 (45882)
28 exp Liver Neoplasms/ (112164)
29 exp Bile Duct Neoplasms/ (11889)
30 Carcinoma, Hepatocellular/ (50647)
31 (FLL or FLLs).ti,ab,ot. (95)
32 Cholangiocarcinoma/ (4109)
33 ((liver$ or hepat$) adj3 (cancer$ or met$ or malignan$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$ or angiosarcoma$)).ti,ab,ot,hw. (168313)
34 (hepatoma$ or h?emangiosarcoma$ or h?emangio-sarcoma$).ti,ab,ot,hw. (27634)
35 (Focal liver lesion$ and (cancer$ or met or mets or metasta$ or malignan$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$ or angiosarcoma$)).ti,ab,ot,hw. (711)
36 (BFLL or BFLLS).ti,ab,ot. (3)
37 (HCC or HCCs).ti,ab,ot. (18590)
38 (Cholangiocarcinoma$ or Cholangio-carcinoma$).ti,ab,ot,hw. (6158)
39 (Bile duct$ adj3 (cancer$ or met$ or malignan$ or lesion$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$)).ti,ab,ot,hw. (14419)
40 or/27-39 (198600)

41 ultrasonography/ or ultrasonography, doppler/ or exp ultrasonography, doppler, duplex/ or exp ultrasonography, doppler, pulsed/ (89506)
42 ((ultrasonic$ or ultra-sonic$) adj4 (scan or imag$ or echogram$ or sonogra$ or detect$ or diagnos$ or exam$)).ti,ot,ab,hw. (6793)
43 (ultraso$ or ultra-so$ or sonogra$ or Echotomogra$ or Echo-tomogra$ or echoscope$ or echosound$ or Echogra$ or tomoechogra$ or tomo-echogra$).ti,ot,ab,hw. (274775)
44 or/41-43 (279114)
45 Sulfur Hexafluoride/ (1474)
46 (hexafluoruro-sulfurico or SF6 or SF-6 or sulphur hexafluoride$ or sulphur hexafluoride$ or sulfur hexafluoride$ or sulfur hexafluoride$).af. (2133)
47 or/45-46 (2133)
48 44 and 47 (658)
49 (Sonovue or sono-vue or Sonavoid or Sonogen or sonagen or Sonavist).af. (499)
50 (CE-US or CEUS).ti,ab,ot. (516)
51 ((hexafluoruro-sulfurico or SF6 or SF-6) adj4 (US or ultraso$ or ultra-so$ or sonogra$ or Echotomogra$ or Echo-tomogra$ or echoscop$ or echosound$ or Echogra$ or tomoechogra$ or tomo-echogra$ or imag$)).af. (7)
52 ((Sulfur or Sulphur) adj2 (hexafluoride$ or hexa-fluoride$) adj4 (US or ultraso$ or ultra-so$ or sonogra$ or Echotomogra$ or Echo-tomogra$ or echoscop$ or echosound$ or Echogra$ or tomoechogra$ or tomo-echogra$ or imag$)).af. (28)
53 (SF6US or SF6-US or SF-6US or SF-6-US).af. (0)
54 ((SF6 or SF6 or sulphur hexafluoride$ or sulphur hexafluoride$ or sulfur hexafluoride$ or sulfur hexafluoride$) adj4 (bubbl$ or microbubbl$ or micro-bubbl$ or micropartic$ or micro-partic$)).af. (213)
55 or/49-54 (991)
56 48 or 55 (1183)
57 40 and 56 (365)
58 exp Liver Neoplasms/us (2702)
59 Carcinoma, Hepatocellular/us (1258)
60 exp Bile Duct Neoplasms/us (375)
61 Cholangiocarcinoma/us (137)
62 Neoplasm Metastasis/us (51)
63 Neoplasm Seeding/ra (1)
64 Neoplasms, Unknown Primary/us (21)
65 or/58-64 (3089)
66 47 and 65 (162)
67 57 or 66 (366)
68 limit 67 to yr="2000 -Current" (361)
69 animals/ not (animals/ and humans/) (3586762)
70 68 not 69 (340)
**71 22 and 70 (19)**

Economics filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

**Appendix 2**

**NICE guidelines on interventions for the treatment of liver malignancies.**

Cryotherapy for the treatment of metastases. NICE interventional procedure guidance 369 (2010). Available from
http://guidance.nice.org.uk/IPG369

Ex-vivo hepatic resection and reimplantation for liver cancer. NICE interventional procedure guidance 298 (2009). Available from
http://guidance.nice.org.uk/IPG298

Laparoscopic liver resection. NICE interventional procedure guidance 135 (2005). Available from
http://guidance.nice.org.uk/IPG135

Microwave ablation for the treatment of liver metastases. NICE interventional procedure guidance 406 (2011). Available from
http://guidance.nice.org.uk/IPG406

Microwave ablation of hepatocellular carcinoma. NICE interventional procedure guidance 214 (2007). Available from
http://guidance.nice.org.uk/IPG214

Radiofrequency ablation of hepatocellular carcinoma. NICE interventional procedure guidance 2 (2003). Available from
http://guidance.nice.org.uk/IPG2

Radiofrequency-assisted liver resection. NICE interventional procedure guidance 211 (2007). Available from
http://guidance.nice.org.uk/IPG211

Selective internal radiation therapy for non-resectable colorectal metastases in the liver. NICE interventional procedure guidance 401 (2011). Available from
http://guidance.nice.org.uk/IPG401

## Appendix 3

## Draft model structure

Different types of FLL have not yet been included in this structure. This information could be added, if evidence is available.

There seems to be reasonable possibility of detecting false test results in the course of treatment/follow up. This is not yet incorporated in the model, but may potentially influence the outcomes of the analysis considerably.

Direct health effects of the diagnostic procedures are not yet included, this could be done if relevant.